

**UNITED STATES DEPARTMENT OF COMMERCE****United States Patent and Trademark Office**Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
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| APPLICATION NO. | FILING DATE | VOLUME | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|-----------------|-------------|--------|----------------------|---------------------|
| 10/22/01        | 07/25/01    | W-1    |                      |                     |

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 PRIMARY EXAMINER ART UNIT  PAPER NUMBER

07/25/01

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

**Commissioner of Patents and Trademarks**

|   |                                      |                                     |
|---|--------------------------------------|-------------------------------------|
| <b>Office Action Summary</b>  | Application No.<br><b>08/940,692</b> | Applicant(s)<br><b>Valle et al.</b> |
|   | Examiner<br><b>Rebecca Prouty</b>    | Art Unit<br><b>1652</b>             |
|    |                                      |                                     |
| <i>-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --</i>  |                                      |                                     |
| <b>Period for Reply</b>   |                                      |                                     |
| <p>A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE <u>3</u> MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.</p>   |                                      |                                     |
| <ul style="list-style-type: none"> <li>- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.</li> <li>- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.</li> <li>- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.</li> <li>- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).</li> <li>- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).</li> </ul> |                                      |                                     |
| <b>Status</b>   |                                      |                                     |
| 1) <input checked="" type="checkbox"/> Responsive to communication(s) filed on <u>7-10-00 and 5-31-01</u>   |                                      |                                     |
| 2a) <input checked="" type="checkbox"/> This action is FINAL.      2b) <input type="checkbox"/> This action is non-final.   |                                      |                                     |
| 3) <input type="checkbox"/> Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under <i>Ex parte Quayle</i> 1035 C.D. 11; 453 O.G. 213.   |                                      |                                     |
| <b>Disposition of Claims</b>  |                                      |                                     |
| 4) <input checked="" type="checkbox"/> Claim(s) <u>23-31 and 33-46</u> is/are pending in the application.   |                                      |                                     |
| 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.   |                                      |                                     |
| 5) <input type="checkbox"/> Claim(s) _____ is/are allowed.  |                                      |                                     |
| 6) <input checked="" type="checkbox"/> Claim(s) <u>23-31, 33-38, 41, 42, and 44-46</u> is/are rejected.   |                                      |                                     |
| 7) <input checked="" type="checkbox"/> Claim(s) <u>39, 40, and 43</u> is/are objected to.   |                                      |                                     |
| 8) <input type="checkbox"/> Claims _____ are subject to restriction and/or election requirement.  |                                      |                                     |
| <b>Application Papers</b>   |                                      |                                     |
| 9) <input type="checkbox"/> The specification is objected to by the Examiner.   |                                      |                                     |
| 10) <input type="checkbox"/> The drawing(s) filed on _____ is/are objected to by the Examiner.  |                                      |                                     |
| 11) <input type="checkbox"/> The proposed drawing correction filed on _____ is: a) <input type="checkbox"/> approved b) <input type="checkbox"/> disapproved.   |                                      |                                     |
| 12) <input type="checkbox"/> The oath or declaration is objected to by the Examiner.  |                                      |                                     |
| <b>Priority under 35 U.S.C. § 119</b>   |                                      |                                     |
| 13) <input type="checkbox"/> Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).  |                                      |                                     |
| a) <input type="checkbox"/> All b) <input type="checkbox"/> Some* c) <input type="checkbox"/> None of:  |                                      |                                     |
| 1. <input type="checkbox"/> Certified copies of the priority documents have been received.  |                                      |                                     |
| 2. <input type="checkbox"/> Certified copies of the priority documents have been received in Application No. _____.   |                                      |                                     |
| 3. <input type="checkbox"/> Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  |                                      |                                     |
| *See the attached detailed Office action for a list of the certified copies not received.   |                                      |                                     |
| 14) <input type="checkbox"/> Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).   |                                      |                                     |
| <b>Attachment(s)</b>  |                                      |                                     |
| 15) <input type="checkbox"/> Notice of References Cited (PTO-892)   |                                      |                                     |
| 16) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   |                                      |                                     |
| 17) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s). <u>26</u>   |                                      |                                     |
| 18) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____   |                                      |                                     |
| 19) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)  |                                      |                                     |
| 20) <input type="checkbox"/> Other: _____   |                                      |                                     |

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Claims 1-22 and 32 have been canceled. Claims 23-31, 33-39 and 40-46 are still at issue and are present for examination.

Applicants' arguments filed on 7-10-00 and 5-31-01, paper Nos. 25 and 27 respectively, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not

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commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 23, 27, 28, 38, 41, 45, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saier et al and Ingrahm et al.

Saier et al. teach methods of selecting a Pts<sup>-</sup>/glucose<sup>+</sup> cell comprising deleting the PTS genes (*ptsH* and *ptsI*), culturing the mutant cell using glucose as the sole available carbon source and selecting cells with a fast growth rate on glucose. The fastest growth rate specifically obtained by the mutants of Saier et al. was 0.35/hr. Applicants claimed methods recite selecting cells with a growth rate of at least 0.4/hr.

Ingrahm et al. teach that it would be advantageous to increase the supply of PEP in a cell used for production of a desired product, in particular aromatic amino acid production, by modifying an enteric bacteria such as *E. coli* to use an alternative pathway from the PTS system for glucose uptake such that PEP production is not obligately coupled to glucose transport.

Therefore, as Ingrahm et al. disclose that Pts<sup>-</sup>/glucose<sup>+</sup> cells are particularly useful for production of desired products one of ordinary skill in the art would have been motivated to

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screen for Pts<sup>-</sup>/glucose<sup>+</sup> cells such as those of Saier et al. with even higher growth rates than those specifically disclosed by Saier et al. As Saier et al. disclose cells with growth rates very close to the claimed rate of at least 0.4/hr one of ordinary skill in the art would have reasonably expected to be able to obtain cells within the scope of the claims.

Claims 23-31, 33-38, 41, 42, 44, 45, and 46 are rejected under 35 U.S.C. § 103 as being unpatentable over the combined disclosures of Frost, Holms, Ingrahm et al. and Saier et al. The rejection is explained in the previous Office Action.

Applicant's argue that the 103 rejection should be withdrawn as the cited references fail to provide sufficient motivation to increase PEP availability. This is not persuasive because Ingrahm et al. specifically suggest preventing PEP use by the PTS system (while providing another means of glucose transport) as an approach to increasing the carbon flow into the common aromatic pathway. Ingrahm et al. state in column 1:

"Phosphoenol pyruvate (PEP) is a central intermediate in glucose metabolism, residing at a branch point for the biosynthesis of many compounds of commercial importance. For example, an equimolar amount of PEP is combined with erythrose-4-phosphate to provide the carbon skeleton for aromatic products such as tyrosine, phenylalanine, tryptophan, and some vitamins among other compounds."

and further go on to state:

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"In many bacteria, PEP is also necessary for the transport of glucose into the cell. Glucose is phosphorylated in a concerted process by a multiprotein-membrane-bound complex termed the phosphotransferase system (PTS). In this process, PEP serves as the source of a high energy phosphate which is ultimately attached to glucose to yield glucose-6-phosphate and pyruvate. During glycolysis in these organisms, half the PEP produced is obligately consumed to provide energy for glucose uptake. This reduces by 50% the amount of PEP available as a source of carbon skeletons for biosynthesis, severely impacting the efficiency of conversion into many desired commercial products."

Finally in column 3, Ingrahm et al. state:

"For example, by modifying an enteric bacteria such as *E. coli* to use an alternative pathway for glucose uptake characteristic of *Z. mobilis*, the output of any synthetic product derived from PEP as a precursor could be doubled because glucose transport into cells would not be obligately coupled to PEP."

Therefore, Ingrahm et al. explicitly suggest the uncoupling of glucose transport and PEP utilization as a means of increasing the carbon flow into the common aromatic pathway. While Ingrahm et al. suggest doing this by a different means than that suggested by applicants, Saier et al. clearly teach that other means of providing glucose transport to a PTS<sup>-</sup> cell are known in the art. As such it would have been obvious to one of ordinary skill in the art that the same objective explicitly stated in Ingrahm et al. could be provided by the PTS<sup>-</sup>/glu<sup>+</sup> cells of Saier et al.

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Claims 39, 40, and 43 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

These claims are limited to cells having a specific growth rate of at least 0.8/hr or methods of using such cells. Saier et al. fail to teach that one can obtain PTS<sup>-</sup>/glu<sup>+</sup> cells with a growth rate this high. While one of ordinary skill in the art would clearly have been motivated to look for cells with higher growth rates than those obtained by Saier et al. (as discussed above), the ordinary skilled artisan would expect that limitations on the ability of the cell to transport glucose might inhibit the rate of growth of the cells on this sugar such that one could not reasonably expect that cells with such a substantially higher growth rate could be obtained without a demonstration thereof. As such it would have merely been obvious to try to obtain cells with this claimed higher growth rate.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Rebecca Prouty  
Primary Examiner  
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